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(54) Title: PROCESS FOR PREPARING CONTROLLED-RELEASE DIHYDROPYRIDINE COMPOSITIONS

(57) Abstract

Disclosed is a process for the preparation of a controlled-release pharmaceutical composition to be suspended in liquids, suitable for the administration of active ingredients having a dihydropyridine structure and, in particular, of nifedipine. This procedure permits a convenient application of dihydropyridines on microgranules suitable to be formulated in pharmaceutical compositions that permit administration to the patient in the liquid form. Also disclosed is a pharmaceutical composition prepared by said process.

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PROCESS FOR PREPARING CONTROLLED-RELEASE DIHYDROPYRIDINE COMPOSITIONS

Field of the invention

The invention relates to a procedure for the preparation of controlled-release pharmaceutical compositions for suspension in liquids, suitable for the administration of dihydropyridine calcium channel antagonist compounds and compositions obtained by such process.

Background of the invention

Nifedipine and other dihydropyridine calcium channel antagonist compounds such as, for example, amlodipine, lacidipine, nicardipine, lercanidipine, and nitrendipine, are compounds known to be extremely useful in the treatment of hypertension and coronary disease.

Only a few of these dihydropyridine calcium channel antagonist compounds are available in dosage forms suitable for once-daily administration, either because they possess a sufficiently long *in vivo* metabolic half-life (for example amlodipine) or because of inherent pharmacodynamic characteristics (for example lercanidipine). Conversely, other dihydropyridine calcium channel antagonist compounds such as nifedipine, nicardipine, and nimodipine, have a short half-life which, when fast-release formulations are administered, can require three or more daily doses in order to maintain therapeutically effective levels of drug in a subject's bloodstream.

In addition to the problems associated with the therapeutic use of some of these dihydropyridine calcium channel antagonist compounds, in particular nifedipine, due to their low solubility, sensitivity to light, and low bioavailability, there also exists another serious problem posed by the immediate-release, liquid or soft-gelatin-capsule formulations normally used to administer these drugs. Use of these fast-release formulations poses a safety risk for patients taking the drugs because of the high blood levels of the compounds which may be achieved immediately after administration. For example, Furberg et al. (Circulation, 92,

1326-1331 (1995) and JAMA. 274, (8), 620-625 (1995)) demonstrated the danger involved in the use of short-acting nifedipine formulations. These formulations, especially at high doses, may induce an increased risk of myocardial infarction, due to the rapid increase in blood concentration of the dihydropyridine calcium channel antagonist compound to supratherapeutic levels.

The problem can be minimized or eliminated when formulations designed to control (i.e., slow) the release of the drug are administered.

Numerous examples in the literature describe controlled-release formulations for dihydropyridine calcium channel antagonist compounds. For example, U.S. Patent 5,252,337 describes the preparation of microcapsules for the controlled release of nifedipine or other dihydropyridine calcium channel antagonist compounds. EP 526,862 describes bioadhesive preparations for the administration of drugs comprised of a high-density material to improve the bioavailability of nifedipine and other active ingredients. EP 385,582 describes nifedipine compositions having a particular particle size. U.S. patent 5,108,757 describes tablets obtained from a granulate which was sprayed with a solution of nifedipine together with a wetting and release-retarding agent.

On the one hand, these formulations provide for safe (i.e., controlled-release) administration of dihydropyridine calcium channel antagonist compounds. However, the mode and timing of administration of these formulations also create problems of compliance and dosage flexibility, which, given the predominantly elderly population which typically takes dihydropyridine calcium channel antagonist compounds for hypertension and other coronary diseases, are significant disadvantages.

It is known that the administration of solid dosage forms to elderly subjects or subjects who have had a stroke can involve compliance problems because these dosage forms are difficult to swallow. Swallowing problems can be significantly reduced when liquids are administered. On the other hand, existing liquid formulations of dihydropyridine calcium channel antagonist compounds such as, for example, nifedipine drops, do not permit a controlled-release administration of the drug.

Thus, there is clearly a recognized need in the art for liquid controlled-release formulations for the administration of antihypertensive dihydropyridine calcium channel antagonist compounds, where such formulations combine the benefits of better compliance achievable with liquid dosage forms and the therapeutic benefits of controlled-release formulations.

U.S. Patent 5,296,236 describes a formulation consisting of microgranules containing active ingredient dispersed in a solid form, such microgranules being coated with a series of film-forming materials capable of modulating the release of the active ingredient and preserving the active ingredient's stability after the microgranules have been suspended in an aqueous vehicle.

However, the disclosure of U.S. Patent 5,296,236 also teaches that the active ingredient of the composition must be intimately mixed and granulated together with the excipients which make up the microgranules. This method, particularly in the case of active ingredients that possess poor stability, can lead to reactions which degrade the active ingredient. Furthermore, when the active ingredients are to be administered in low-dosages, maximizing the yield of the industrial manufacturing process becomes important.

Summary of the invention

It has now unexpectedly been found that it is possible to obtain controlled-release liquid suspension preparations using a procedure where the active ingredient, e.g., a dihydropyridine calcium channel antagonist compound, rather than being mixed with microgranulated excipients, is applied as a solution or a dispersion on an inert microgranular nucleus comprised only of excipients, provided that the microgranular form is endowed with appropriate characteristics which make it suitable for film-coating. The microgranular nuclei coated with the active ingredient can then be further coated with film-forming materials which are capable of modulating the release rate of the active ingredient in a pharmacologically desirable manner.

According to the process of the invention, a solution and/or suspension of an active ingredient can be applied to an inert microgranular nucleus which has been previously screened to the required size. This avoids the need to regranulate the

microgranule fractions which are outside the desired dimensional limits, thus improving production yield. Furthermore, the method is particularly beneficial in the case of low-dose and poor-chemical-stability active ingredients. This is because it is during the regranulation step required by the processes of the prior art that active ingredients are most often, and most easily, degraded.

Experimental tests conducted in humans showed that nifedipine plasma levels obtained by administering a controlled-release liquid suspension prepared according to the method of preparation of the present invention are comparable with those obtained by administering the controlled-release solid preparations already available in the market.

Therefore, the present invention provides a novel procedure for the preparation of slow-release pharmaceutical compositions suitable for the oral administration of dihydropyridine calcium channel antagonist compounds, in particular nifedipine, and the pharmaceutical composition prepared by such process.

This procedure entails an initial coating of a microgranule consisting solely of excipients with active ingredient dissolved or suspended in an appropriate solvent, followed by one or more successive coatings of the resulting active ingredient-coated microgranules with layers of film-forming materials capable of controlling the release rate of the active ingredient after administration to a subject.

The microgranules coated as described above can then be combined with common vehicles suitable for the preparation of oral liquid suspensions. The microgranules of the invention are suitable for preparing suspensions for reconstitution immediately before use, as well as suspensions remaining stable throughout the period after reconstitution and before administration. Alternatively, the microgranules of the invention can be used to prepare ready-to-use suspensions which do not require reconstitution.

Brief description of the drawing

Figure 1 is a graph which shows the steady-state plasma levels of nifedipine (Conc. (ng/mL)) obtained by administering FORMULATION A (diamonds) or B (circles)

either on an empty stomach (dotted lines) or after food intake (solid lines) over time (hours).

Detailed description of the invention

As used herein, a "controlled-release" pharmaceutical composition is a composition that can either maintain constant plasma levels of active agent after administration of the composition, or which can prolong therapeutic blood levels of active agent for an extended period of time relative to conventional, fast release compositions.

The invention provides a process for the preparation of a controlled-release pharmaceutical composition according to the invention for the administration of dihydropyridine calcium channel antagonist compounds, which is suitable for suspension and administration in liquids. The process comprises the following steps:

a)granulating excipients to provide microgranules having diameters ranging from 50 to 500 mm, preferably from 125 to 315 μm, said microgranules having a substantially spherical shape;

b) applying a first coating layer uniformly to the surface of said microgranules, said coating layer comprising a dihydropyridine calcium channel antagonist compound;

c)applying a second coating layer over said first coating layer to form a pH insensitive barrier, said second coating layer being capable of controlling the release rate of said dihydropyridine calcium channel antagonist compound;

d) applying at least two successive coating layers comprised of alternating hydrophilic and lipophilic layers over said second coating layer, said hydrophilic and lipophilic layers being capable of controlling the release rate of said dihydropyridine calcium channel antagonist compound.

In a preferred embodiment, the microgranular controlled-release pharmaceutical composition according to the invention is combined with a vehicle system, which vehicle system can be made up of:

a)a dry mixture of suspending agents and sweeteners, which when combined with the microgranular controlled-release pharmaceutical composition results in a dry

formulation which can be reconstituted by the patient immediately before administration;

b)a dry mixture of suspending agents, sweeteners and preservatives, which when combined with the microgranular controlled-release pharmaceutical composition results in a formulation that can be reconstituted with water by the patient and stored as a liquid suspension, where the liquid suspension maintains controlled-release properties during storage. That is, the controlled-release properties of the microgranular controlled-release pharmaceutical composition is stable in aqueous solution, and upon reconstitution can be used for immediate administration as well as subsequent administration, until such time as administration is terminated or the liquid suspension has been consumed; or

c)an aqueous solution of suspending agents, sweeteners, and preservatives, where the coated controlled-release microgranules are suspended during manufacture and maintain their controlled-release properties during storage and use, i.e., for at least two years.

Another aspect of the present invention is a kit comprising at least a pharmaceutical composition according to the invention, preferably in form of dry formulation or in form of suspension, and optionally at least a liquid for the reconstitution of the liquid formulation before administration, said reconstitution being easy to be prepared by the patient.

The kit according to the invention can comprise the pharmaceutical composition in dry formulation or in form of suspension presented as multidose bottle, single-dose package, single dose bottle or ready-to-use suspension. When the suspension is in form of single-dose packages, they are preferably paper, aluminum or polyethylene packages.

The present invention also relates to an effective amount of the pharmaceutical composition according to the invention for use in therapy, preferably for the treatment of cardiovascular disease.

The present invention further relates to the use of dihydropyridine calcium channel antagonist compound for the manufacture of a controlled-release pharmaceutical composition for the treatment of cardiovascular disease.

A. Preparation of the Microgranules

The excipients used for obtaining the microgranules to be coated with active ingredient can be chosen from those commonly used in a wet mixture, such as lactose, dibasic calcium phosphate, microcrystalline cellulose, starch, talc, sugars, polyvinylpyrrolidone, gelatin, a polyvinylpyrrolidone-vinylacetate copolymer and the like.

The addition of compounds such as polyethylene glycol (PEG), and in particular PEG 6000, can useful in the preparation of the microgranular nucleus. The mixing liquid to be used for wet granulation, for example in high-speed kneader-granulators, may be water or a solvent miscible with water such as, for example, ethyl alcohol, or other alcohols used in the pharmaceutical industry or any mixture thereof with water.

The mixing and granulating operating conditions required to obtain a microgranulate that is an optimal substrate for coating according to the present invention are described in U.S. patent 5,480,828.

After the microgranular excipient nucleus is dried and screened, the active ingredient is applied onto the microgranular nucleus. The active ingredient-coated microgranular nucleus is then coated with film-coats of various compositions using known film-coating methods.

B. Application of Active Ingredient

An active ingredient such as nifedipine, or other dihydropyridine calcium channel antagonist compounds, can be dissolved in a suitable solvent such as acetone or ethanol, or can be suspended in a mixture of an organic solvent and water. Dihydropyridine calcium channel antagonist compounds are known in the art, and are defined herein as those compounds which comprise a dihydropyridine structural nucleus and possess the property of antagonizing, i.e., blocking, calcium ion channels when administered to mammals. Such compounds include nifedipine,

amlodipine, lacidipine, nicardipine, isradipine, felodipine, nimodipine, lercanidipine, and nitrendipine, and the like. Such dihydropyridine compounds, and their properties, are described, e.g., in *Goodman & Gilman's The Pharmacological Basis of Therapeutics,* 9th Ed., J.G. Hardman, L.E. Limbird, P.B. Molinoff, R.W. Ruddon, and A.G. Gilman, Eds., Chapter 32, pp. 767-772, 1996.

The addition of binding compounds such as hydroxypropylcellulose, hydroxypropylmethylcellulose or polyethylene glycols can be useful to layer the active ingredient on the microgranular excipient nucleus.

The solution and/or suspension of the active ingredient is then applied onto the microgranular excipient nucleus using a spray system in a fluid-bed apparatus such as those described in the Examples below.

C. Successive Film-Coating Layers

The compounds suitable for the first film-coating layer, which is applied directly on the active ingredient, is intended to form a barrier insensitive to pH changes, and can include derivatives of cellulose, acrylic or methacrylic polymers to which plasticizers can be added, such as diethyl phthalate, triethylcitrate, dibutyl sebacate, vegetable oils and the like.

The compounds suitable for the second coating layer, which has hydrophilic characteristics, can be hydrophilic derivatives of cellulose, in particular cellulose acetophthalate or hydroxypropylmethylcellulose phthalate, and acrylic and methacrylic polymers. Plasticizers can optionally be added to the second, hydrophilic coating layer, such as diethyl phthalate, triethylcitrate, dibutyl sebacate, vegetable oils and the like.

The compounds suitable for the third coating layer, which has lipophilic characteristics, include fatty compounds such as mono-, di- or triglycerides of fatty acids having a chain with 6 to 36 carbon atoms, carnauba wax, beeswax, candelilla wax, fatty alcohols and fatty acids. These can be applied either in solution using chlorinated solvents or in the melted state, which allows application without the use of solvents.

The compounds making up the second coating layer can also be used for the third coating layer.

D. Vehicle

The active-ingredient containing microgranules coated according to the above described methods can be combined with a vehicle to form a mixture of the two granulates which can be suspended in water, i.e., reconstituted, at the time of administration. The vehicle can also be made up of a mixture of excipients which permit a ready-to-use suspension to be produced.

The constituent elements of the vehicle include:

- suspending and structuring agents such as cellulose esters and ethers, microcrystalline cellulose, alginic acid derivatives, polyvinylpyrrolidone derivatives, natural gums, and the like;
- sugars such as saccharose, sorbitol, xylitol, dextrose and the like;
- buffering compounds such as citric acid and sodium citrate, glycine and hydrochloric acid, sodium and potassium phosphates, and the like;
- preservatives and bacteriostats such as the esters of p-hydroxybenzoic acid, sorbic acid and its salts and the like;
- various flavors, wetting agents, and sweeteners commonly used in pharmaceutics.

In addition to the above elements, the dosage form to be delivered ready for use also includes water or mixtures of water and co-solvents miscible with water such as glycols, alcohols and glycerin.

The following non-limiting Examples are comprised of methods, tables, and graphs intended to better explain the subject invention and demonstrate its advantages and applicability.

EXAMPLE 1: Preparation of basic placebo nucleus (placebo microgranules)

A mixture made up of 4050 g of micronized lactose and 450 g of polyvinylpyrrolidone (PVP K 30) was mixed for 5 minutes. A 0.8 mm Glatt nozzle set for a flow rate of 20 g/minute was then fitted onto the cover of a Fielder high-speed kneader/granulator (Nitro-Fielder Mayflower, Eastleigh Hampshire, England). 400 ml of water atomized at a pressure of 0.5 bars was added to the stirred mixture and the

granulate was then further kneaded and made spherical for 20 minutes at a speed of 200 rpm. The granulate was removed and dried in an oven at 45°C for 1.50 hours and then screened using a Russel shaking sifter apparatus (Russel Finex Ltd., Feltham Middlesex, England) to obtain a particle-size fraction ranging from 125 to 315 mm in diameter.

EXAMPLE 2: Application of nicardipine on placebo microgranulate

1200 g of a 10% (w/w) suspension of nicardipine dispersed in a 50/50 mixture of ethanol/water was applied onto 2400 g of a placebo microgranulate prepared in accordance with Example 1. The suspension was immediately sprayed using a 7-inch Wurster insert in a Glatt GPCG-3 fluid-bed apparatus (Glatt GmbH, Binzen Lorrach, Germany).. After the application of nicardipine, the microgranulate was coated with a film of ethylcellulose followed by a film of waxy material and finally a film of cellulose acetophthalate.

EXAMPLE 3: Application of nifedipine on placebo microgranulate

1233 g of a solution of micronized nifedipine dissolved in 11% acetone (w/w) was applied to 2400 g of a placebo microgranulate prepared according to Example 1. The application was performed spraying the nifedipine solution by means of a 1.2-mm nozzle in a Glatt GPCG-3 fluid-bed apparatus equipped with a 7-inch Wurster film-coating insert. The working conditions included: air flow-rate 23-28 m^3/hour, inlet air temperature 40-45°C, atomizing pressure 1 bar, outlet air temperature 30-37°C, product temperature 34-40°C, pump flow-rate 8-14 g/min. The microgranulate surface area after the application of nifedipine, calculated on the basis of the particle-size analysis and density, ranged from 250 to 350 cm^2/g.

EXAMPLE 4: Coating of nifedipine microgranulate with ethylcellulose

735 g of a solution having the following composition:

ethylcellulose N22	3.0%
diethyl phthalate	1.0%
polyethylene glycol 400	0.1%
95% ethanol	95.9%

was sprayed onto 1500 g of a microgranulate coated with nifedipine according to Examples 1 and 3. The film-coating was performed using a GPCG-3 fluid-bed apparatus with a 6-inch Wurster insert, into which air heated to a temperature of 55°C was blown at a pressure of 2 bars and a flow-rate of 11 g/minute using a nozzle.

EXAMPLE 5: Coating with cellulose acetophthalate (hydrophilic coating)

A hydrophilic coating of cellulose acetophthalate was applied onto 1250 g of film-coated granulate according to Example 4, using the same type of equipment and procedure. 300 ml of a solution having the following per-cent composition:

cellulose acetophthalate	4.0
diethyl phthalate	1.0
isopropyl alcohol	23.7
acetone	71.3

was sprayed at a pressure of 2 bars and a flow rate of 8 to 10 g/min.

EXAMPLE 6: Coating with a waxy mixture (lipophilic coating)

120 g of a waxy mixture having the following per-cent composition (w/w):

glyceryl monostearate	90.0
beeswax	8
stearyl alcohol	1
cetyl alcohol	1

was applied to the film-coated granulate from Example 5 according to the procedure described above.

The waxes were first melted in an oil bath at a temperature of 120°C and then applied maintaining the temperature at about 80°C with compressed air (pre-heated to 135°C) at a pressure of 3 bars by means of a coaxial nozzle which permitted mixing of melted waxes and compressed air. A Glatt GPCG-3 apparatus with a 6-inch Wurster insert was used for this operation. The sprayed waxes were equivalent to 3.8% by weight of the microgranulate after application of nifedipine. A spraying rate of 2.5 g/minute was used.

EXAMPLE 7: Final coating

Ingredients, percentages and procedures identical to those described in Example 5 were used for the final coating, which was intended to allow effective wetting of microgranules.

EXAMPLE 8: Vehicle composition and presentations

A) Suspension in multidose bottles

A mixture made up of microcrystalline cellulose and sodium carboxymethylcellulose (Avicel™ 611) 3.16%, tribasic sodium citrate bihydrate 0.94%, citric acid monohydrate 0.8%, tragacanth 0.94%, sodium lauryl sulfate 0.09%, dimethyl polysiloxane 0.02%, orange-grapefruit flavor 0.25% and sorbitol P100 T q.s. to 100%, was added to a slow-release microgranulate (14.7%) prepared according to Examples 3, 4, 5 and 7. 57 g of water was added to 63.98 g of this mixture and 100 ml of a suspension containing 4 mg/ml of nifedipine was obtained.

B) Suspension in single-dose packages

4.7 g of a suspension mixture prepared as described at paragraph A) was divided into paper/aluminum/polyethylene packages. Each package contained 30 mg of nifedipine and could be re-suspended in half a glass of water (50 ml).

C) Suspension in single-dose bottles

0.706 g of a slow-release microgranulate prepared according to Examples 3, 4, 5 and 7 was transferred into a compartment under the cap of a single-dose bottle (Bormioli) and was kept separate from the liquid contained in the bottle. The composition of the single-dose liquid included 70% sorbitol 3500 mg, pineapple-lemon flavour 15 mg, citric acid 15 mg, sodium benzoate 10 mg, purified water q.s. to 8 ml. Before use, the contents of the cap compartment were put in contact with the liquid in the bottle by pressing on the cap compartment. Each bottle contained 30 mg of nifedipine as a single-dose suspension.

D) Ready-to-use suspension

9.80 g of a slow-release granulate prepared according to Examples 3, 4, 5 and 7, was dispersed in a suspension vehicle having the following composition: 70% sorbitol 67.50 g, glycerine 11.80 g, mannitol 4.00 g, citric acid 0.01 g, potassium

sorbate 0.15 g, sodium lauryl sulphate 0.1 g, avicel CL 611 1.00 g, xanthan gum 0.12 g, titanium dioxide 0.50 g, 10% simethicone 0.10 g, orange flavour 0.15 g, water 26.68 g. The suspension was prepared by dissolving mannitol in half a liter of water and then dispersing avicel CL 611, glycerine, xanthan gum and half of the sorbitol in the solution. Citric acid, potassium sorbate, sodium lauryl sulfate and simethicone were dissolved separately and titanium dioxide was dispersed in the solution. The two suspensions were combined and the slow-release granulate and the remaining sorbitol were added to the combined suspensions. After mixing the orange flavor was added.

EXAMPLE 9: In vitro dissolution

The release properties of the microgranules coated with nifedipine and prepared according to Examples 1, 3, 4, 5, 6 and 7 are shown below. Determinations were made using the "Paddle" apparatus II described by the U.S. Pharmacopoeia XXIII at page 1792, operating with 900 ml of water, at 50 revolutions per minute, at 37°C and in a pH gradient, to which 2% of Texapon™ N40 was added. The amount of active ingredient was determined by HPLC collecting 5 ml of the solution at pre-established times. The dissolution data are shown in Table 1.

TABLE 1

TIME (hours)	NIFEDIPINE RELEASED (%)
1	1.4
2	9
4	25
8	62
12	86
24	100

EXAMPLE 10: Bioavailability in humans

The bioavailability and pharmacokinetic profile of an exemplary formulation of the present invention were determined in "in vivo" single-dose and repeated-dose clinical studies, also evaluating the effect of food intake on changes in these parameters.

A) Single-dose study

A single-dose study was conducted in 6 healthy volunteers using a formulation prepared with nifedipine applied on a microgranular placebo and then coated with film-forming material according to Examples 1, 3, 4, 5, 6 and 7 (FORMULATION A). The reference compound was a controlled-release tablet which acted via an osmotic system (Procardia XL^{R} 30 mg, also known as ADALAT-CRONO^{R}) (FORMULATION B).

Each patient received 5 ml of a suspension of FORMULATION A equal to 20 mg of nifedipine and a tablet of FORMULATION B equal to 30 mg of active ingredient, at different times. Blood samples were taken at different times and the plasma concentrations of nifedipine were determined by HPLC. Table 2 shows the main pharmacokinetic parameters obtained from the test.

TABLE 2

FORMULATIONS	C_{max}(ng/ml)	T_{max}(hours)	$AUC_{0-\infty}$ (ng /ml)
A	7.05	6.7	97.0
B	10.45	12.3	138.6

where:

C_{max}=(peak concentration) is the highest concentration reached by the drug in plasma after dosing;

T_{max}=(peak time) is the time required to reach the level of C_{max};

$AUC_{0-\infty}$ =(area under the curve) is the total area under the time-concentration curve and represents a measure of the bioavailability of the drug

These data show that, taking into account the different doses, the properties of the two formulations are comparable with respect to the main pharmacokinetic parameters.

B) Multiple-dose study and food effect

A repeated-dose study was conducted in 6 healthy volunteers for 7 days by administration of either FORMULATION A or B described in the above single-dose study. The effect of food on nifedipine release and absorption was also evaluated in the multiple-dose study.

Blood samples were taken at different times and the nifedipine plasma concentrations were determined by an HPLC method. The results are shown in Figure 1, which shows the steady-state plasma levels obtained by administering one of FORMULATION A or B either on an empty stomach (dotted lines) or after food intake (solid lines). Figure 1 shows the nifedipine plasma concentrations (ng/ml) as the ordinate and the time (hours) as the abscissa.

The graph shows that the controlled-release liquid-suspension formulation provides a constant pharmacokinetic profile which prevents the side effects associated with immediate-release formulations. The formulation of the present invention can, therefore, be considered equivalent, with respect to pharmacological performance, to the best controlled-release solid formulations currently available (Procardia XL - FORMULATION B). However, the formulation of the present invention ALSO possesses the benefits which are peculiar to liquid formulations, for example ease of swallowing and dosage flexibility, due to the ability to administer any desired volume of liquid suspension, as opposed to the relatively fixed dose in a solid dosage form.

CLAIMS

1. A process for the preparation of a controlled-release pharmaceutical composition, said controlled-release pharmaceutical composition being suitable for administration of dihydropyridine calcium channel antagonist compounds in a liquid suspension formulation, said process comprising:

a) granulating excipients to provide microgranules having diameters ranging from 50 to 500 mm, said microgranules having a substantially spherical shape;

b) applying a first coating layer uniformly to the surface of said microgranules, said coating layer comprising a dihydropyridine calcium channel antagonist compound;

c) applying a second coating layer over said first coating layer to form a pH insensitive barrier, said second coating layer being capable of controlling the release rate of said dihydropyridine calcium channel antagonist compound;

d) applying at least two successive coating layers comprised of alternating hydrophilic and lipophilic layers over said second coating layer, said hydrophilic and lipophilic layers being capable of controlling the release rate of said dihydropyridine calcium channel antagonist compound.

2. The process of claim 1, wherein said excipients include a mixture of polyethylene glycol and at least one member selected from the group consisting of polyvinylpyrrolidone, lactose, dibasic calcium phosphate, microcrystalline cellulose, starch, talc, sugars, polyvinylpyrrolidone/vinylacetate copolymer and gelatin.

3. The process of claim 1, wherein said dihydropyridine calcium channel antagonist compound has a metabolic half-life in humans shorter than 8 hours.

4. The process of claim 3, wherein said dihydropyridine calcium channel antagonist compound is selected from the group consisting of nifedipine, nicardipine and nimodipine.

5. The process of claim 1, wherein said second coating is comprised of one or more materials selected from the group consisting of cellulose derivatives, derivatives of acrylic or methacrylic polymers, and optionally one or more plasticizers selected from the group consisting of diethyl phthalate, triethylcitrate, dibutyl sebacate, and vegetable oils.

6. The process of claim 1, wherein said hydrophilic coating layers in step d) are comprised of compounds selected from the group consisting of cellulose acetophthalate and hydroxypropylmethylcellulose phthalate, acrylic polymers and derivatives, methacrylic polymers and derivatives, and optionally one or more plasticizers selected from the group consisting of diethyl phthalate, triethylcitrate, dibutyl sebacate and vegetable oils.

7. The process of claim 1, wherein said lipophilic coating layers in step d) are comprised of materials selected from the group consisting of saturated mono-, di- or triglycerides, fatty acids, fatty alcohols, esters of propylene glycol, esters of saccharose, and waxes.

8. The process of claim 2, wherein said coating layers are applied onto said microgranules as solutions, suspensions or in the melted state using a fluid-bed apparatus.

9. The process of claim 1, wherein said controlled-release pharmaceutical composition is admixed with a vehicle system to provide a dry formulation, said dry formulation being suitable for admixture with water to provide a liquid suspension formulation.

10. The process of claim 9, wherein said vehicle system is a member selected from the group consisting of:

a) a dry mixture of suspending agents and sweeteners, wherein said dry formulation is suitable for reconstitution with water by a patient to provide a liquid suspension immediately before administration; and

b) a dry mixture of suspending agents, sweeteners and preservatives, wherein said dry formulation can be reconstituted with water by a patient and stored as a liquid suspension, wherein said liquid suspension maintains controlled-release properties during storage.

11. The process of claim 1, wherein said controlled-release pharmaceutical composition is admixed with a vehicle system comprising a liquid component, suspending agents, sweeteners, and preservatives to provide a liquid suspension formulation, wherein said controlled-release pharmaceutical composition maintains

controlled-release properties during storage and use of said liquid suspension formulation.

12. The process of claim 11, wherein said liquid component of said vehicle system is comprised of water and, optionally, co-solvents miscible with water, said co-solvents selected from the group consisting of glycols, alcohols and glycerin.

13. The process of claim 1 wherein said microgranules have diameters from 125 to 315 mm.

14. A controlled-release pharmaceutical composition prepared according to the process of claims 1-13.

15. An effective amount of the composition according to claim 14 for use in therapy.

16. An effective amount of the composition according to claim 15, for the treatment of cardiovascular disease.

17. Use of dihydropyridine calcium channel antagonist compound for the manufacture of a controlled-release pharmaceutical composition for the treatment of cardiovascular disease.

18. A kit comprising at least a pharmaceutical composition according claim 14, and optionally at least a liquid for the reconstitution of the liquid formulation before administration.

19. A kit according to claim 18 wherein the pharmaceutical composition is in form of dry formulation or in form of suspension.

20. A kit according to claims 18-19, wherein the pharmaceutical composition is in form of multidose bottle, single-dose package, single dose bottle or ready-to-use suspension.

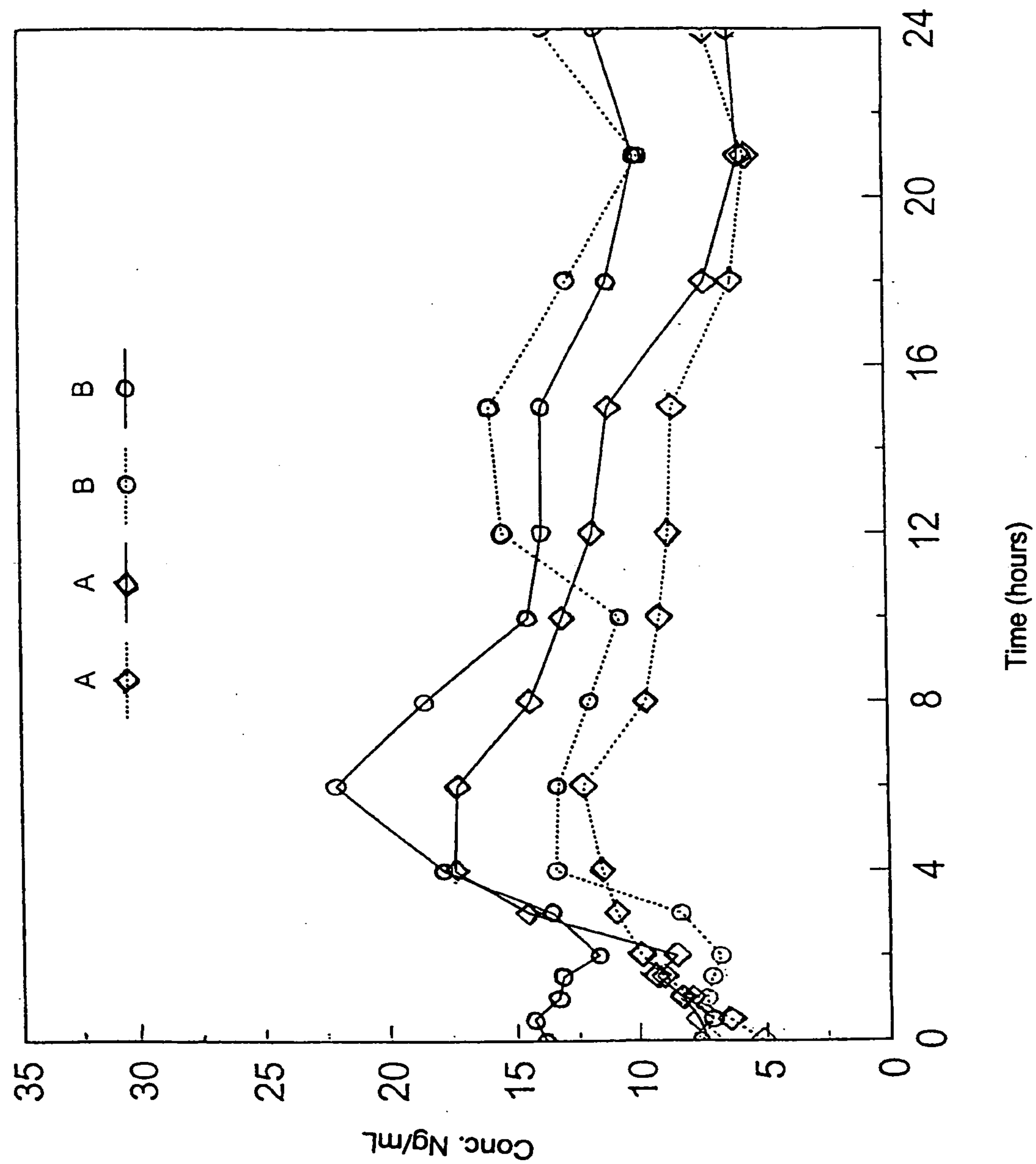

FIGURE 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/03982

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44 A61K9/54 A61K9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 296 236 A (GOLZI ROBERTO ET AL) 22 March 1994 cited in the application see column 2, line 32-47 see column 3, line 7-17 see column 3, line 53 - column 4, line 37 see column 5, line 3 - column 6, line 47 see claims ---	1,14,18
A	US 4 758 437 A (SONOBE TAKASHI ET AL) 19 July 1988 see column 1, line 10-15 see column 2, line 23-50 see column 2, line 55 - column 3, line 15 see examples 2,5 see claims --- -/--	1,14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 October 1998	03/11/1998

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 05262 A (FAULDING F H & CO LTD ;MORELLA ANGELO MARIO (AU); QUINN EUGENE ANT) 17 March 1994 see page 3, line 17-25 see page 10, line 10-27 see page 11, line 5-20 see page 11, line 34 - page 12, line 38 -----	1,14

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